Division of Air Quality

Summary of the toxicity assessment of vinyl acetate conducted by the Secretary's Scientific Advisory Board on Toxic Air Pollutants

Abstract

The Secretary's Scientific Advisory Board on Toxic Air Pollutants (SAB) evaluated the toxicity of vinyl acetate in response to a request made by the Division of Air Quality. Vinyl acetate is emitted in significant quantities in North Carolina and was not considered by the North Carolina Academy of Sciences in 1986. Vinyl acetate is used to produce polymers found in such products as adhesives, paints, textiles and paper products. Sufficient exposure to airborne vinyl acetate may produce a variety of toxic effects in humans including eye, nose and throat irritation. In rats, prolonged exposures resulted in the appearance of nasal cavity tumors. This, and the fact that some known metabolites of vinyl acetate are capable of causing DNA damage, indicates that vinyl acetate may possess carcinogenic properties in humans.

The SAB considered several published studies related to the toxicity of vinyl acetate and engaged in extended discussions with experts in the area of vinyl acetate toxicology before issuing their exposure guideline recommendations. The SAB's recommendations are based on chronic toxicity and carcinogenicity in rats following prolonged inhalation exposure to vinyl acetate. The Board agreed to endorse two proposals. The first is centered on a mechanism of action scheme involving nasal tissue lesions that may progress to tumors later in life. Mathematical dose-response modeling was utilized to establish a theoretical "no effect level" or "benchmark dose" (ED_{10}) for these pre-cancerous lesions. The SAB then applied uncertainty factors to this value to reach their final exposure recommendation. The second approach is based solely on tumor incidence. The SAB calculated a tumor benchmark dose and then drew a straight line from that point on the dose-response curve to the origin. The SAB used this exercise to define the exposure level that would theoretically cause an increased cancer incidence rate of 1 in 10,000 individuals over a lifetime of exposure. Both recommendations utilized a recently completed physiologically-based pharmacokinetic (PBPK) model as the basis for predicting adverse effect levels in humans using animal data. The finalized recommendations for vinyl acetate were issued at the 67th meeting of the SAB. *These recommendations should be considered two separate options and only one should be moved forward to the rule-making phase.* The ultimate choice of which recommendation to forward is to be made by the Environmental Management Commission.

More detailed information on the use of PBPK models and benchmark doses is contained within this summary.

Data Assessment

Human Toxicity Data: Humans are primarily exposed to airborne vinyl acetate in occupational settings. Limited short-term exposure studies have been carried out with human volunteers [1]. These studies and other workplace studies demonstrated that airborne vinyl acetate is irritating to the eyes and respiratory tract at levels as low as approximately 20 ppm [2]. When workplace exposures were kept below 10 ppm, no complaints of eye irritation were documented. At present there is not sufficient information to assess the chronic toxicity or carcinogenicity of vinyl acetate in exposed humans.

According to the EPA's Toxics Release Inventory, over 123,000 lbs. of vinyl acetate was emitted in 1996 into the air in North Carolina.

Animal Toxicity Data: Several animal studies of acute or sub-chronic nature have been performed involving inhalation or drinking water exposures to vinyl acetate. Drinking water studies failed to demonstrate significant adverse effects in rats exposed below 1000 ppm [3]. In mice similarly treated, toxic effects were absent at doses as high as 5000 ppm [3]. Like humans, laboratory animals seem to be susceptible to the short-term irritant properties of vinyl acetate when exposed through the air [1,3]. Rats exposed for 4 weeks to 500 ppm vinyl acetate showed signs of respiratory tract irritation. These effects were not seen at 150 ppm [3]. At 200 ppm, vinyl acetate is a pulmonary irritant to exposed mice, but exposure to 50 ppm fails to produce a significant toxicologic effect, following 3 months of exposure [3]. Dogs exposed to 186 ppm vinyl acetate for 1 week showed signs of eye irritation, but were not visibly affected by exposure to 91 ppm for 6 weeks [4].

In chronic (lifetime) drinking water studies, no adverse effects were seen in rats provided drinking water containing 1000 ppm vinyl acetate. At 5000 ppm, depressed weight gain was observed [5]. Chronic inhalation studies involving rats and mice demonstrated adverse effects at concentrations as low as 200 ppm, but not at 50 ppm. These effects were generally limited to the respiratory tract and appeared to be related to chronic pulmonary and nasal cavity tissue irritation. Non-cancerous adverse effects noted in both species include olfactory epithelial atrophy and altered tissue regeneration at 200 ppm. These effects increased in incidence and severity in the 600 ppm group. Toxic effects in the lung were primarily seen only in the 600 ppm exposure groups [6].

Animal Cancer Data: The International Agency for Research of Cancer has designated vinyl acetate as "*possibly carcinogenic to humans* (*Group 2B*)" based on limited evidence in experimental animals and inadequate human evidence [7]. Vinyl acetate does not appear capable of inducing point mutations in DNA, but it does give rise to chromosomal damage in several *in vitro* studies [7]. Acetaldehyde, a primary metabolite of vinyl acetate, is capable of causing direct DNA damage [7]. The ability to cause DNA damage is suggestive evidence that an agent carries cancer-causing potential.

Laboratory animal cancer studies with vinyl acetate have produced variable results. In one study involving lifetime exposures to drinking water containing up to 2500 ppm vinyl acetate, significant increases in uterine and thyroid tumors were detected in female rats at the highest dose level [8]. However, decomposition of vinyl acetate in the drinking water medium may have confounded the results of that study. In a more recent drinking water study, vinyl acetate did not produce significant increases in cancer, even at concentrations as high as 5000 ppm [5].

When administered to rats via the inhalation route of exposure, vinyl acetate is carcinogenic at 600

ppm, but not 200 ppm. A total of 11 animals out of 119 exposed were affected with nasal tissue tumors in the 600 ppm exposure group vs. 0/118, 0/119 and 1/120 in the 0 ppm, 50 ppm, and 200 ppm exposure groups, respectively. Of the 12 total nasal tumors identified, 7 were confirmed as malignant. There was no statistically significant increase in tumor incidence at any other site in the rat. No significant increase in treatment-related tumors was detected in mice similarly exposed to vinyl acetate [(6)].

Following a review of the toxicological database for vinyl acetate, the SAB concluded that this rodent inhalation cancer study would serve as the most appropriate basis for a quantitative assessment of risk from inhalation of vinyl acetate.

Modeling the Potential Risk for Humans Exposed to Vinyl Acetate

Physiologically-Based Pharmacokinetic Modeling: Within the risk assessment community there has been a concerted effort to create models that will shed light on the relationship between adverse effects in experimental animals and possible adverse effects in exposed humans. Historically, potential differences in the susceptibility of exposed species have been accounted for in risk assessments with safety or uncertainty factors. Often, this is a conservative method that presupposes humans will be up to an order-of-magnitude more sensitive to the toxic effects of an agent than experimental animals. By incorporating as extensively as possible available information on relevant pathways of metabolism and disposition of a given toxicant and the physiology of the affected organisms, one can create a model that more accurately accounts for differences in species susceptibility. This information can then be used to relate experimental exposures to internal dosimeters (measures of effect) in different species, reducing the need for uncertainty factors. These models are referred to as physiologically-based pharmacokinetic (PBPK) models. They are playing an increasingly important role in quantitative risk assessments.

Recently, a sophisticated PBPK model for vinyl acetate has been completed by a group of scientists from DuPont's Haskell Laboratory and the Vinyl Acetate Toxicology Group [(9)]. The model focuses on the mode-of-action behind the nasal tissue effects documented in the most recent rodent inhalation study [(6)]. Important parameters in the model include human and rodent enzyme distribution and activity levels, respiratory rates, airstream partitioning, and tissue surface areas and pH. The model was used to determine appropriate dosimeters for interspecies extrapolation. Once established, these dosimeters are then related to effective external exposure concentrations for human beings. The PBPK model was presented to the SAB during their consideration of vinyl acetate.

The most critical "parameter" in the PBPK model is the proposed mode of action for vinyl acetate. The main author of the vinyl acetate chronic inhalation study and PBPK model, Dr. Matthew Bogdanffy of DuPont, made several visits before the Board to discuss the chronic inhalation study, the PBPK model, and the mode of action proposal (refer to SAB proceedings #58-65). Dr. Bogdanffy presented a mode of action scheme that involves a mechanistic link between non-cancerous lesions that develop in the nasal cavity in the intermediate and high dose groups and tumors that develop at those locations in the high dose groups. He argued that the nasal lesions result from significant localized metabolism of vinyl acetate to acetic acid, which then overwhelms the tissue's ability to control intracellular pH (the chosen dosimeter). Because the enzyme responsible for this metabolism is highly active in nasal passages, damage is primarily confined to these tissues [(9)].

Dr. Bogdanffy successfully convinced the SAB that his proposed scenario was logical and

appropriately presented, but before the SAB would incorporate it into a calculation of risk they undertook a thorough review of the fine points in the model. With few exceptions they found the model parameters to be suitable. Only human breathing rates were modified. The Board asked that the model parameters be adjusted to incorporate the most recent estimates published by the EPA [10]. Once the Board was satisfied that the appropriate adjustments had been made to the model, they agreed to incorporate it in their final risk calculations to account for potential differences in species susceptibility.

Benchmark Dose Analyses: As with many toxicological studies, the chronic rodent inhalation study involved relatively high levels of exposure to vinyl acetate and high rates of cancer incidence. The goal of the SAB was to utilize this experimental data to predict a dose that would pose minimal carcinogenic risk. Several mathematical and statistical methods currently exist for undertaking this effort.

The authors of the vinyl acetate PBPK model presented a "benchmark dose" model that can be used to approximate low-dose effects from high-dose experimental data. This approach has been gaining wide acceptance in the risk assessment community and is increasingly being used by the EPA. The strength of the benchmark dose concept is its more thorough use of the full range of experimental data. In the past, quantitative risk assessments have been based on the lowest identified toxic dose (LOAEL) or lowest dose at which no effect was detected (NOAEL). These values were then decreased to safe exposure levels through the use of uncertainty factors of up to 30,000. Experimental dose setting obviously plays a critical role in this exercise and can result in widely disparate final safe dose estimates for the same agent, depending on which study is used as the basis for the risk assessment. Using benchmark doses, this problem can be circumvented because the target effect dose (ED), or benchmark dose, is modeled rather than defined experimentally. Using the full range of experimental data, a dose-response curve is generated with an appropriate mathematical model. The benchmark dose is then estimated as a point on this curve (usually a 10% response is desired, thus the benchmark dose would be defined as the ED_{10}). The benchmark dose replaces the NOAEL or LOAEL as the starting point in quantitative risk assessments. Wider use of the benchmark dose concept should encourage better study design in the future and decrease uncertainty in quantitative risk assessments [11].

The EPA has indicated an interest in defining the benchmark dose as the "LED_{10}," which represents the lower 95% confidence limit on the modeled 10% response dose [12]. The ED_{10}, by comparison, is the *central estimate* of the 10% response rate; the best-guess approximation of the dose that would cause a 10% incidence of adverse effect, as modeled from a given dataset. Use of the LED_{10} (rather than the ED_{10}) is defended with the argument that experimental design and variability may contribute to fluctuations in predicted response rates. Using the lower 95% confidence limit assures that this estimate is highly unlikely to underestimate the actual 10% response dose. On the other hand, it also adds another level of conservatism that may or may not increase the accuracy of the prediction.

Because the SAB felt the vinyl acetate study was of high quality, they concluded that the central estimate of the benchmark dose (ED) would be appropriate for vinyl acetate benchmark dose exercises. The SAB took two approaches to calculating risk from vinyl acetate during the course of their review. These approaches both involved calculating benchmark doses, but the nature of the benchmark dose varied somewhat. The first approach, centered around a "margin of exposure" calculation, utilized the modeled 10% toxic response rate (ED_{10}). The second calculation involved

identifying the lowest statistically defensible benchmark dose (ED_{04}) for tumor incidence and using that point as the spring-off for a linear extrapolation to the origin.

For further discussion on the use of benchmark doses in quantitative risk assessments, one should refer to EPA's 1996 *Proposed Guidelines for Carcinogen Risk Assessment* [12] or other related publications [11].

Vinyl Acetate Risk Calculations

The SAB established their policies concerning the use of the benchmark dose during their review of vinyl acetate. Dr. Bogdanffy was able to produce the benchmark doses requested by the SAB for use in their risk calculations. The Board agreed to incorporate Dr. Bogdanffy's PBPK model into their quantitative assessments of risk, believing it made the best use of the available data and represented a reasonable mode-of-action proposal. In essence, the PBPK model was used in place of a default uncertainty factor of 10 to calculate the difference in species susceptibility.

Approach #1. At the Board's request, Dr. Bogdanffy instructed the model to estimate the dose at which 10% of the rats would be afflicted with "olfactory precursor lesions." The effective dose for rats was established by defining parameters relating to metabolism of vinyl acetate to acetaldehyde and acetic acid, which may then cause derangement of intracellular pH, cellular toxicity and eventual tumor development. This ED_{10} was then adjusted to represent continuous exposure by accounting for the non-continuous exposures involved in the study. The experimental design involved 6-hour exposures, 5 days per week, which represents approximately 18% of the potential exposure time (24 hours per day, 7 days per week). Thus, the modeled ED_{10} was multiplied by the ratio of possible hours exposed to actual hours exposed. This calculation provided the theoretical rat ED_{10}, adjusted for continuous exposure.

Dr. Bogdanffy then instructed the PBPK model to generate the equivalent external exposure dose for humans. The dosimeter chosen was significant alteration of cellular pH [9]. The calculation of equivalent human exposure values involves the use of several experimentally determined human physiological parameters, including breathing rates and metabolic factors. The Board asked that Dr. Bogdanffy modify the model assumptions slightly to incorporate a more realistic human breathing rate for adult males [10]. Use of breathing rates for this segment of the population should provide protection for all other segments of the population including women, children and the elderly. The Board did not express reservation with any other parameter contained in the PBPK model.

Consistent with a "margin of exposure" approach, the Board applied uncertainty factors, as necessary, to the human ED_{10}. Since much of the uncertainty related to susceptibility between species was addressed through the use of the PBPK model, it was decided that an explicit uncertainty factor for this was not needed. However, while acknowledging that the mode of action behind the PBPK model was plausible and well supported by empirical evidence the Board concluded that an uncertainty factor of 2 should be included, to account for the possibility that fundamental assumptions behind the model were in error. The use of this safety factor is documented in the guidelines for safety and uncertainty factors used by the SAB [13]. The Board also concluded that a safety factor of 10 should be implemented to account for potential differences in susceptibility between humans. Variability inherent in the human population may render some individuals more susceptible to the toxic effects of vinyl

acetate. The overall safety factor of 20 was applied to the modified human ED_{10} to generate an acceptable exposure concentration for vinyl acetate. It can be reasonably assumed that chronic human exposure to vinyl acetate at this concentration will not result in nasal lesions that may be precursors to cancer.

Approach #2. Using a benchmark dose calculation and linear low-dose extrapolation, the SAB completed a risk assessment for vinyl acetate that establishes an exposure level that is estimated to cause an increase in cancer incidence of 1 case in 10,000 (1×10^{-4}) persons exposed. This exercise involved 1) defining the lowest statistically stable rodent benchmark dose for tumor incidence (in this case the ED_{04}), 2) calculating the rodent 1×10^{-4} risk level by extrapolating from the ED_{04} to the origin with a linear low-dose model, 3) modifying that value to generate an estimate for continuous exposure, and 4) applying the PBPK model to generate the corresponding predicted value for humans (see calculation #2, below).

The target risk value of 1×10^{-4} is used when the agent in question is designated as *possibly carcinogenic to humans* and the available experimental data is suitable for the assessment of low-dose effects [13]. The calculation in approach #2 differs from approach #1 in that the toxic endpoint in question is the development of tumors rather than development of non-cancerous lesions that may be precursors to tumors. It also uses an assumption of low-dose linearity, which is the appropriate default methodology if the evidence for an exclusively non-linear mode of action is not convincing.

Conclusion

The SAB reviewed the current toxicological literature for vinyl acetate and concluded the most recent round of rodent lifetime inhalation exposure studies would be the best basis for assessing human health risks from exposure to airborne vinyl acetate. Through continuous interaction with the study authors they were able to generate risk calculations that incorporate elements of a new vinyl acetate PBPK model. They also incorporated benchmark dose methods, using two different approaches to calculate safe exposure levels. The first recommendation utilizes a margin-of-exposure approach to set a final safe exposure value that should result be protective against the development of chronic olfactory tissue irritation. The second approach is based on tumor incidence rather than olfactory lesion incidence and uses a linear extrapolation from the lowest statistically stable benchmark dose to the origin to establish the dose that represents a "one in ten thousand" risk level for tumor incidence.

The SAB agreed to present both risk estimates as a fulfillment of the recommendation by the Air Toxics Working Group that they forward a range of risk estimates rather than one single estimate. The SAB cannot state with certainty which risk assessment technique is more accurate or appropriate. Practically speaking, while the two recommendations are based on different toxicological endpoints, they should both result in protection against chronic effects such as tissue irritation and cancer. However, if one were not swayed by the proposal that vinyl acetate acts exclusively via a cytotoxic mode of action, then choosing approach #2 would be preferred.

Averaging Time

The Division of Air Quality recommends that a 24-hour averaging time be applied if approach #1 is chosen. This recommendation is consistent with the guidelines detailed by the North Carolina Academy of Sciences, which prescribes 24-hour averaging times for chemicals associated with adverse

effects only after multiple or prolonged exposures (14). If approach #2 is chosen, an annual averaging time should be attached. This recommendation is consistent with guidelines that prescribe an annual averaging time when tumor incidence is considered (14).

Calculations

Two approaches:

1. margin-of-exposure, ED_{10} for precursor lesions
2. linear extrapolation, ED_{04}-driven to 1×10^{-4} incidence rate for tumors

1: PB/PK-driven benchmark dose approach, precursor lesion incidence

Study: Bogdanffy, et al, 1994; Plowchalk, et al, 1997; VATG report

Endpoint: Modeled intracellular ΔpH

Method: Log-logistic model, β restricted to greater than or equal to 1.0

Estimated external exposure concentration

Aolfactory precursor lesions@ - tumors + pre-cancerous lesions

Human parameters included for final estimate of risk, based on PBPK

model predictions for intracellular pH change.

$\underline{ED_{10}}$

Rat external exposure: 60.7 ppm

(C x T) correction[1]: 10.8 ppm

Human equivalent concentration (PBPK): 11.5 ppm (15.2 m^3/day breathing rate)[2]

Uncertainty factor correction[3]: **0.58 ppm** (15.2 m^3/day breathing rate)

2: Neoplastic response, tumor benchmark with linear extrapolation to 10^{-4} risk level

Study: Bogdanffy, et al, 1994

Log-logistic model, low-dose linear extrapolation from ED_{04}

Endpoints of concern: Total nasal tumors (olfactory + respiratory)

Rat ED_{04}: 410 ppm

1×10^{-4} risk level

Rat external exposure: 1.0 ppm

(C x T) correction[1]: 0.18 ppm

Human equivalent concentration (PBPK): **0.13 ppm** (15.2 m^3/day breathing rate)

[1] Time correction factor = (6 hrs / 24 hrs) x (5 days / 7 days) = 0.18

[2] EPA adult male average daily breathing rate (1997 Exposure Factors Handbook)

[3] Total safety factor = 20 (10 for variability between humans, 2 for model uncertainty)

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